PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Susan J. CLARK et al Conf. No.: **5339**

Appln. No.: **09/673,448** Group Art Unit: **1634**

Filed: **October 16, 2000** Examiner: **Goldberg, J.A.**

For: **ASSAY FOR METHYLATION IN THE GST-Pi GENE**

RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner
of Patents
Washington, D.C. 20231

Sir:

This Response to Restriction Requirement is in reply to the Office Action dated February 27, 2002, for which a Petition for a Three-Month Extension of Time, along with payment of the appropriate fee, is attached, making reply is on or before June 27, 2002.

REMARKS

In paragraph 1, on page 2 of the Office Action, the Examiner issued a Restriction Requirement under 35 U.S.C. §§ 121 and 372 to one of the invention of the following groups:

Group I - Claims 1-48, drawn to a diagnostic assay; or

Group II - Claims 49-50, drawn to nucleic acid probes and primers for the GST Pi gene.

Accordingly, Applicants hereby elect the invention of Group I, i.e., Claims 1-48, with traverse.

The Examiner asserts that the assay of Claims 1-48 is not linked with the probes and primers of Claims 49-50 so as to form a single inventive concept under article PCT Rule 13.1.

The Examiner is requested to note that the present application is a Rule 371 of Australian Application PP 3129.

PCT Rule 13.2 provides:

> Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Applicants respectfully submit that, contrary to the Examiner's contention, the present claims to the assay share a "special technical feature" with the claims directed to the probes and primers.

The Examiner asserts that the special technical feature of the method of Claim 1 "is drawn to the GST Pi gene" and that the "GST Pi gene is not a contribution over the prior art".

Applicants respectfully submit that the Examiner's analysis ignores the fact that Claim 1 defines, as a feature of the assay of the invention, "...the amplification [is] selective in that it only amplifies the target region if the said site or sites at which abnormal cytosine methylation occurs is/are methylated". Applicants respectfully submit that the latter feature forms part of the "special technical feature" of the invention defined in present Claim 1.

The Examiner goes on to state that the method of Claim 1 does not appear to be a contribution over the prior art, citing Lee et al as an example. The Examiner asserts that Lee et al teaches CG island methylation changes near the GST Pi gene in prostatic carcinoma cells detected using PCR. The Examiner particularly refers to page 443, column 2 of Lee et al which is said to describe the isolation of DNA followed by "amplification using PCR primers of set A and the PCR products were electrophoresed to determine the presence". The Examiner further notes that the amplifying step targeted a region within the GST-Pi gene and its regulatory flanking sequence.

While Lee et al may refer to the use of PCR in the detection of CG island methylation changes near the GST-Pi gene, the method actually described involves "exhaustive digestion with *Hpa*II" prior to amplification using PCR (see page 443, column 2, "Materials and Methods"). Furthermore, the description of Fig. 1 at page 444 indicates that:

> ...in prostate cells, but not normal cells, extensive deoxycytidine hypermethylation would render the CG island encompassing the GST PI 5' regulatory region DNA (21) refractory to digestion by *Hpa*II. As a result, prostate cancer cell DNA, but not normal cell DNA, would readily yield applification products...

Thus, Lee et al does <u>not</u> teach a PCR assay that "[is] selective in that it <u>only</u> amplifies the target region if the said site or sites at which abnormal cytosine methylation occurs is/are methylated", as claimed in the present application. On the contrary, Lee et al teaches the skilled reader that amplification using PCR must take place <u>after</u> the DNA sample

taken from a subject is subjected to extensive digestion. Thus, the method of Claim 1 is clearly patentable over Lee et al.

As for Jhaveri, the Examiner concludes that it "appears to teach a method which involves amplification of CpG islands within the GST PI gene". However, Jhaveri describes the use of Southern blot analysis to determine the methylation status of the CpG island. The only apparent reference in Jhaveri to the use of PCR is in the determination of the effect of partial demethylation of the CpG island by treatment with 5-aza-deoxycytidine. Applicants submit that Jhaveri does not teach or suggest an assay that "[is] selective in that it only amplifies the target region if the said site or sites at which abnormal cytosine methylation occurs is/are methylated", as required by present Claim 1. Thus, the method of present Claim 1 is clearly patentable over Jhaveri.

Turning to Claims 49-50, these claims are directed to primers or probes of at least 19 nucleotides. Applicants respectfully submit that the Examiner's conclusion that these claims encompass the full length gene is not based on a proper construction of the claims. The nucleotide sequences defined in Claims 49-50, when used in amplification of DNA in a subject, result in an assay that is selective in tht it only amplifies the target region if the said site or sites at which abnormal cytosine methylation occurs is/are methylated. That is, this "special technical feature" is inherent in the nucleotide sequence of Claims 49-50. This "special technical feature" defines a contribution which each of the claimed

inventions - the assay of Claims 1-48 and the primers/probes of Claims 49-50 - considered as a whole, makes over the prior art.

Accordingly, reconsideration and withdrawal of the Restriction Requirement is hereby requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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